

University of Groningen

Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both (WOMB project)

van de Beek, Corneliëke; Hoek, Annemieke; Painter, Rebecca C.; Gemke, Reinoud J. B. J.; van Poppe, Mireille N. M.; Geelen, Anouk; Groen, Henk; Mol, Ben Willem; Roseboom, Tessa J.

Published in:
BMJ Open

DOI:
[10.1136/bmjopen-2017-016579](https://doi.org/10.1136/bmjopen-2017-016579)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2018

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

van de Beek, C., Hoek, A., Painter, R. C., Gemke, R. J. B. J., van Poppe, M. N. M., Geelen, A., Groen, H., Mol, B. W., & Roseboom, T. J. (2018). Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both (WOMB project): A protocol of the follow-up of a multicentre randomised controlled trial. *BMJ Open*, 8(1), [016579]. <https://doi.org/10.1136/bmjopen-2017-016579>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

BMJ Open Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both (WOMB project): a protocol of the follow-up of a multicentre randomised controlled trial

Cornelieke van de Beek,¹ Annemieke Hoek,² Rebecca C Painter,¹ Reinoud J B J Gemke,³ Mireille N M van Poppel,^{4,5} Anouk Geelen,⁶ Henk Groen,⁷ Ben Willem Mol,^{1,8,9} Tessa J Roseboom¹

To cite: van de Beek C, Hoek A, Painter RC, *et al.* Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both (WOMB project): a protocol of the follow-up of a multicentre randomised controlled trial. *BMJ Open* 2018;**8**:e016579. doi:10.1136/bmjopen-2017-016579

► Prepublication history for this paper is available online. To view these files, please visit the journal online (<http://dx.doi.org/10.1136/bmjopen-2017-016579>).

Received 23 February 2017
Revised 6 November 2017
Accepted 20 November 2017

ABSTRACT

Introduction Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both (WOMB) project is the follow-up of the LIFEstyle study, a randomised controlled trial in obese infertile women, and investigates the effects of a preconception lifestyle intervention on later health of women (WOMB women) and their children (WOMB kids).

Methods and analysis Obese infertile women, aged between 18 and 39 years, were recruited in 23 Dutch fertility clinics between June 2009 and June 2012. The 284 women allocated to the intervention group received a 6-month structured lifestyle programme. The 280 women in the control group received infertility care as usual. 4 to 7 years after inclusion in the trial, all women (n=564) and children conceived during the trial (24 months after randomisation) (n=305 singletons and age 3–5 years) will be approached to participate in this follow-up study (starting in 2015). The main focus of outcome will be cardiovascular health, but the dataset comprises a wide range of physical and mental health measures, diet and physical activity measures, child growth and development measures, biological samples and genetic and epigenetic information. The follow-up assessment consists of three stages that take place between 2016 and 2018, and includes (online) questionnaires, accelerometry and physical and behavioural measurements in a mobile research vehicle. A subsample of 100 women and 100 children are planned for cardiac ultrasound measurements.

Ethics and dissemination The protocol of this follow-up study is approved by the local medical ethics committee (University Medical Centre Groningen). Study findings of the WOMB project will be widely disseminated to the scientific community, healthcare professionals, policy makers, future parents and general public.

Trial registration number The original LIFEstyle study is registered at The Netherlands Trial Registry (number 1530).

INTRODUCTION

The overall aim of the Women, their Offspring and iMproving lifestyle for Better

Strengths and limitations of this study

- The main strength of the Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both project is the fact that it concerns the follow-up of a randomised controlled trial in which a structured lifestyle intervention was given preconceptionally.
- This study provides the opportunity to study the long-term health effects of the intervention on the mother and the prenatal programming effects on her child.
- Reasons to be cautious: attrition will lead to a reduction in power, and there may be selective attrition reducing the representativeness of the study sample.
- The LIFEstyle study women were included as patients with infertility problems which inevitably leads to limitations with respect to the generalisability of the findings to the obese female population in general.

cardiovascular health of both (WOMB) project is to examine the effects of a preconception lifestyle intervention on health in obese women (WOMB women) and their children (WOMB kids). It concerns a follow-up of the LIFEstyle study, a multicentre randomised controlled trial (RCT) (Netherlands Trial Registry number 1530), that was originally set up to investigate the effects and costs of a structured lifestyle programme in overweight and obese infertile couples to prevent unnecessary infertility treatment and improve reproductive outcome.¹ Compared with prompt infertility treatment, the LIFEstyle intervention did not increase the healthy singleton live birth rate, although it did raise the chance of spontaneous conception.² Furthermore, live birth rate was higher



For numbered affiliations see end of article.

Correspondence to

Dr Cornelieke van de Beek;
c.vandebeek@amc.uva.nl

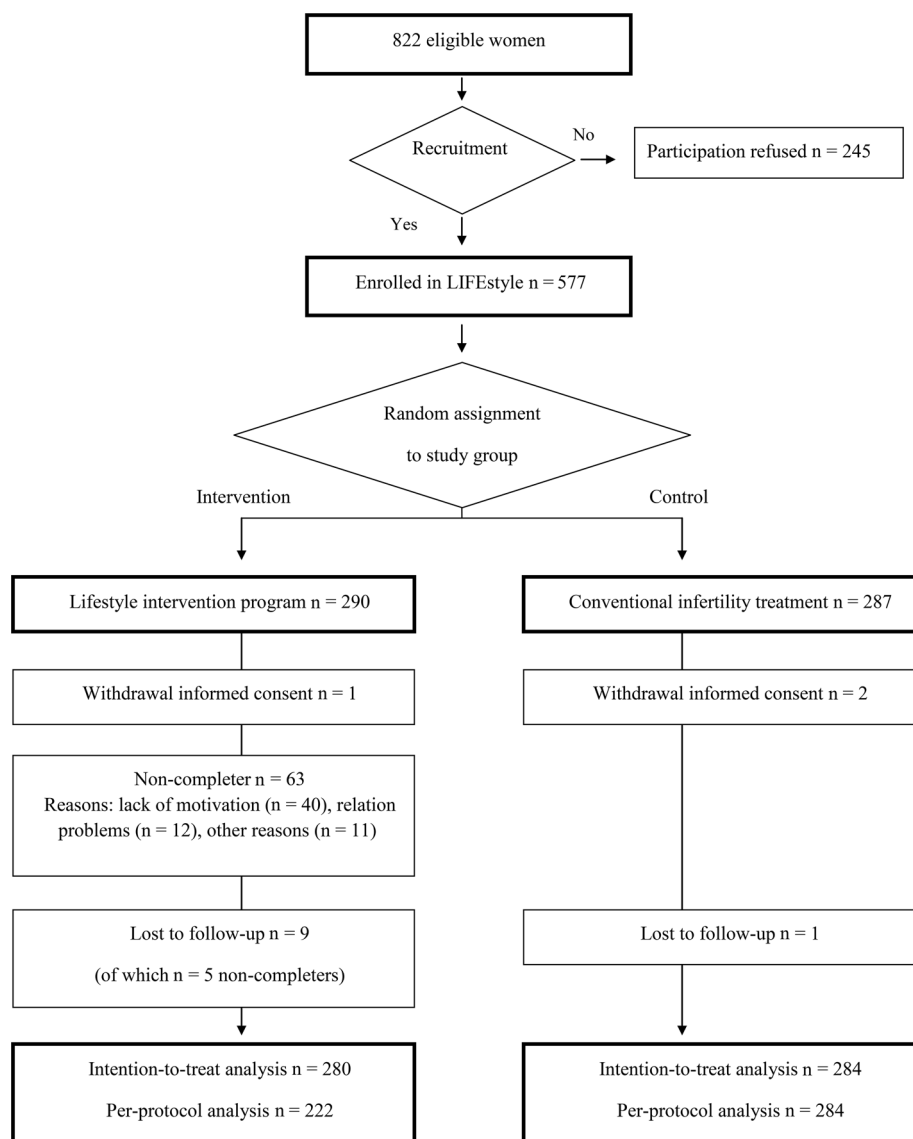


Figure 1 The LIFEstyle flow diagram: recruitment and study design.

in women who succeeded in losing weight.³ Currently, 4–7 years after the LIFEstyle study, we will investigate the effects of the intervention on women's and offspring's lifestyle and health, with specific focus on cardiovascular health.

Overweight and obese women have a higher risk of developing cardiovascular diseases (CVD) compared with normal weight women.⁴ They also have a higher chance of medical and obstetric complications during pregnancy, such as gestational hypertension, pre-eclampsia and gestational diabetes.⁵ The cardiovascular and metabolic health of women before and during pregnancy may influence the development of cardiovascular structure and function, and metabolic balance in the offspring, either mediated by increased risk of obstetric complications or by affecting placental and foetal growth and physiology.⁶ Through these pathways, obese women may transfer the obesity risk to their children by non-Mendelian, for example, epigenetic, mechanisms.⁷

This intergenerational cycle of obesity and consequent susceptibility for non-communicable diseases (NCDs), including CVD, may be broken by improving the health of obese women before and during pregnancy, making a preconceptional lifestyle intervention the ideal window to improve the health of the current and subsequent generations.⁸ In general, women are especially receptive to advice about lifestyle before and during pregnancy^{9 10} and optimising their lifestyle for the benefit of their offspring's health will be a powerful motivator. Therefore, lifestyle interventions before and during pregnancy may be more effective than lifestyle interventions at any other time during the lifespan. Optimising lifestyle of women before and during pregnancy may be an innovative way of improving cardiovascular health and preventing CVD both in women and in their offspring. The design of the LIFEstyle study creates a unique opportunity to investigate the long-term effects of preconception lifestyle advice to overweight and obese women.

Table 1 Baseline characteristics of eligible participants and participants lost to attrition for WOMB women, according to trial group*

Characteristics†	Intervention group		Control group	
	Eligible n=280	Lost to attrition n=10	Eligible n=284	Lost to attrition n=3
Characteristics of woman				
Age (years): mean±SD	28.8±4.5	25.8±3.4	29.8±4.6	30.4±4.8
Caucasian‡	249 (88.9)	8	246 (86.6)	1
Education				
Primary school (4–12 years)	16 (5.7)	1	9 (3.2)	1
Secondary education	67 (23.9)	1	63 (22.2)	1
Intermediate vocational education	129 (46.1)	7	131 (46.1)	0
Higher vocational education and university	55 (19.6)	1	69 (24.3)	1
Unknown	13 (4.6)	0	12 (4.2)	0
Smoker	72 (25.7)	5	60 (21.1)	0
Nulliparous	218 (77.9)	9	215 (75.7)	2
Duration of time attempting to conceive (months): median (IQR)	22.0 (14.0–36.0)	26.5	19.0 (13.0–32.5)	22.0
BMI, median (IQR)	36.0 (33.4–38.5)	34.7	36.0 (33.5–38.2)	39.8
Characteristics of male partner				
Age (years), mean±SD	33.6±6.1	31.1±4.7	33.6±6.2	36.7±9.8
BMI, median (IQR)	27.7 (24.5–31.0)	26.4	27.2 (24.2–31.0)	26.0
Infertility diagnosis§				
Female factor: anovulation	123 (43.9)	5	140 (49.3)	1
Female factor: other	19 (6.8)	10	22 (7.7)	0
Male factor	65 (23.2)	2	64 (22.5)	0
Unexplained	84 (30.0)	3	77 (27.1)	2
PCOS				
PCOS (Rotterdam criteria): number/total number (%)¶	93/123 (75.6)	4/5	104/140 (74.3)	0/1

Differences between the eligible intervention group and the eligible control group were compared with the use of Student's t-test for means, Mann-Whitney U test for medians and χ^2 test or Fisher's exact test for proportions. There were no significant differences between the groups.

*Baseline is at randomisation for the LIFEstyle study.

†Number (%) unless otherwise specified.

‡Ethnic background was self-reported.

§Couples could have more than one diagnosis.

¶The denominator is the number of women with anovulatory infertility.

BMI, body mass index; PCOS, polycystic ovary syndrome; WOMB, Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both.

The LIFEstyle study was performed within the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology. The WOMB project will be carried out in a collaboration between the Academic Medical Centre (coordinating centre), the VU University Medical Centre, the University Medical Centre Groningen and Wageningen University and Research.

METHODS AND ANALYSIS

In the following section, we will adhere to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines to the extent to which it

is possible in a cohort profile. More details on handling of (quantitative) variables and statistical analyses will be provided in the papers describing the findings; the STROBE guidelines will be followed in papers resulting from this study.¹¹

The WOMB cohort consists of women who participated in the LIFEstyle study (WOMB women) and their offspring (WOMB kids).

Participants WOMB women

Between June 2009 and June 2012, women were recruited for the LIFEstyle study at fertility clinics of six university medical centres and 17 general hospitals, spread over

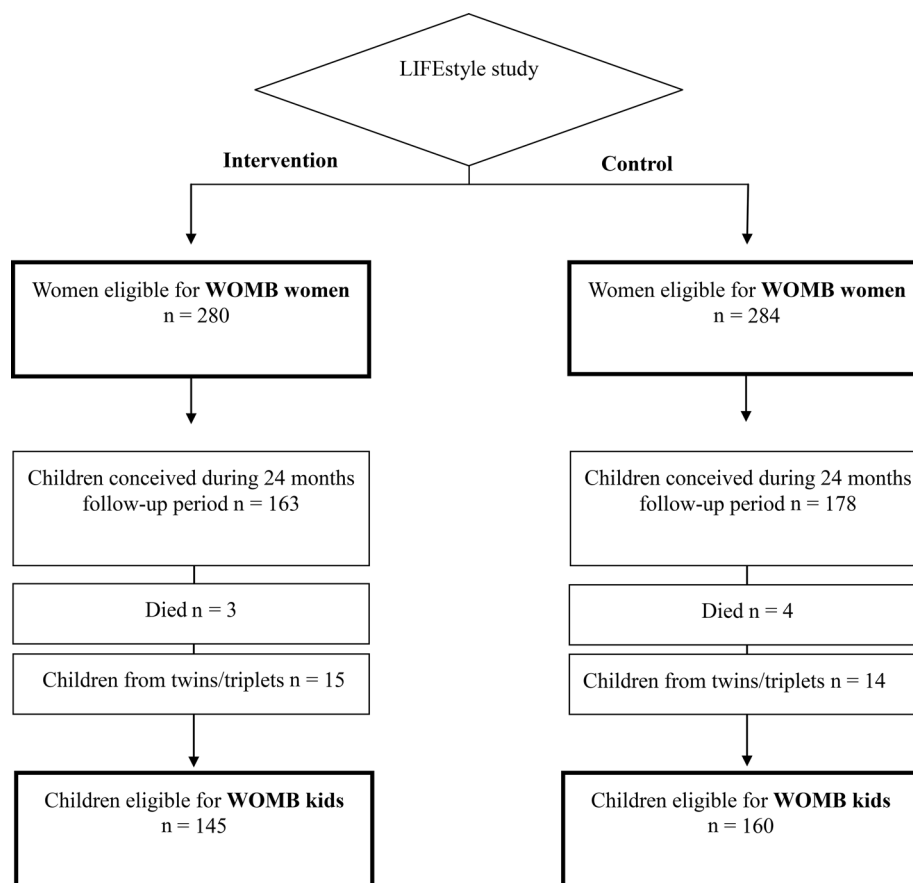


Figure 2 Flow diagram enrolment WOMB women and WOMB kids. WOMB, Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both.

The Netherlands. Women, aged between 18 and 39 years, who presented with infertility and a body mass index (BMI) $\geq 29 \text{ kg/m}^2$ could be included in the study. Women were diagnosed with infertility because of chronic anovulation, oligomenorrhoea or amenorrhoea or, in case of a functioning ovulatory cycle, unsuccessful conception for at least 12 months. Exclusion criteria were severe endometriosis, premature ovarian insufficiency, endocrinopathy (eg, diabetes type I and Cushing's syndrome), the use of donor semen because of azoospermia and untreated preconceptional hypertension or hypertension-related complications in a previous pregnancy.

Of the 822 eligible women, 577 agreed to participate and were randomly assigned to the intervention or the control group after providing written informed consent. Three women withdrew informed consent later on and 10 women were lost to follow-up, leaving 280 women in the control group and 284 women in the intervention group (figure 1). See table 1 for baseline characteristics of both groups.

The 284 women allocated to the intervention group received a 6 months structured lifestyle programme aiming at 5%–10% loss of their original body weight. During this weight loss period, they did not receive infertility treatment. The programme was developed according to National Institutes of Health¹² recommendations during a single centre pilot study.^{13 14} The participants were guided by trained coaches with a degree in nursing or dietetics. Women were

stimulated to reduce energy intake by 600 kcal/day (with a minimum total intake of 1200 kcal/day), supported by an online diet diary.¹⁵ They were also encouraged to increase physical activity, aiming at 10 000 steps per day, monitored by a step counter, and at least 30 min of exercise of moderate intensity two or three times a week. Furthermore, the coaches provided individualised motivational counselling, directed at awareness of healthy lifestyle and formulating goals. The intervention was terminated earlier if women became pregnant. In case of a miscarriage, women could resume the intervention. To enhance compliance with the intervention, the infertility treatment was offered as soon as women had reached minimal 5% wt loss or a BMI $< 29 \text{ kg/m}^2$.

The 280 women in the control group received infertility treatment according to the Dutch infertility guidelines, irrespective of their BMI.

In total, 564 women will be eligible for the follow-up measurements of WOMB women.

Participants WOMB kids

The study population comprises all children of the 564 women eligible for follow-up who were conceived within 24 months after inclusion in the study. In total, 341 children were born of whom 7 children died antepartum, during or short after labour. After exclusion of the children from multiple pregnancies ($n=29$), 305 singletons will be eligible for WOMB kids (figure 2).

Table 2 Measurements of LIFEstyle study

Measures		Timing of assessment*	Data type
Demographic variables (also of partner)	Age, ethnicity, education level and smoking status	0	Self-reported
General health	Medical history	0	Medical record
	Quality of life	0 + 12 + 24 + 52	Self-reported
Anthropometrics	Hip and waist circumference and weight	0 + 12 + 24	Physical examination
Cardiometabolic health	Blood pressure, glucose and insulin levels, lipid profile, inflammatory markers and hormone profile	0 + 12 + 24	Physical examination
Lifestyle	Eating behaviour	0	Self-reported
	Diet (frequency and portion sizes, kcal)†	0 + 12 + 24 + 52	Self-reported
	Physical activity	0 + 12 + 24 + 52	Self-reported and measured by pedometer†
Reproductive health	Previous pregnancies, anovulation, PCOS, infertility and gynaecological history	0	Self-reported and medical record
	Method of conception, infertility treatments and complications	0-104	Medical record
Pregnancy outcomes	Complications (gestational and postpartum maternal), foetal or neonatal outcomes and complications	0-6 weeks after birth	Medical record Self-reported
	Gestational weight gain	0 through birth	
Economic evaluation	Medical costs	0-104 (or 6 weeks after birth in case of pregnancy)	Medical record

*Number of weeks after inclusion, 0=baseline.

†Till 24 weeks in intervention group only.

PCOS, polycystic ovary syndrome.

What has been measured in the LIFEstyle study?

In the LIFEstyle study, information was obtained about demographics, medical, gynaecological and obstetric history, anthropometry, blood pressure, preconceptional lifestyle, eating behaviour, infertility treatment, pregnancy outcome, quality of life and medical costs of the intervention. Blood samples were taken and weight was measured at 0, 3 and 6 months after entering the study. In the intervention group, step counters and dietary assessments were used during the 6 months of the intervention. The majority of these data was collected during the 6 months after inclusion in the study. Key measures are summarised in [table 2](#).

WOMB project: planned follow-up assessments

In the WOMB project, data will be collected about present lifestyle, and mental and physical health, with a specific focus on cardiovascular health. An overview of all key measures is given in [table 3](#) (WOMB women) and [table 4](#) (WOMB kids).

The follow-up assessment consists of three stages (flow-chart in [figure 3](#)) and comprises of (online) questionnaires (focusing on physical and mental health, diet, sleep of woman and child and growth and development of the child), accelerometry, physical measurements and collection of biospecimens (blood, faeces and buccal swab samples) as well as child behavioural observations.

A subsample of 100 women and 100 children are planned for in depth cardiovascular measurements, including intima-media thickness and ultrasound assessment of cardiac function.

The physical measurements and observations are done in a mobile research vehicle in the vicinity of the participants' homes to optimise participation and collect the data in a standardised situation.

Statistical methods and power analyses

Following the RCT design, we will examine the effect of the preconception lifestyle intervention on later lifestyle and health of the women and their offspring by means of intention-to-treat analyses. In addition, we will perform per-protocol analyses in which women who did not complete the intervention will be excluded. Finally, the registered variations in adherence to the prescribed lifestyle intervention will allow us to also perform exploratory dose-response analyses in which associations between measures of variation in diet (eg, fruit/vegetable intake, soft drink intake and snack intake) or physical activity (eg, weekly moderate to vigorous physical activity) will be linked to outcomes (blood pressure, glucose/lipid levels, weight, child development and health) in both short and long term for women and their children. Furthermore, we will investigate whether physical, psychological, socioeconomic or genetic characteristics contribute to the effectiveness of

Table 3 Planned measurements of WOMB women

Phase	Measures		Data type
4–7 years after lifestyle intervention	Demographic variables	Information about current civil status, work and partner	Self-reported
	General health	Diseases/health problems, medication hospital admissions and quality of life	Self-reported
	Anthropometrics	Hip, waist and upper arm circumference, height and weight	Physical examination
	Body composition	Lean body mass, fat mass and total body water	Physical examination
	Cardio metabolic health	Blood pressure, heart rate, arterial stiffness, ECG, physical condition, glucose and insulin levels, lipid profile and inflammatory markers	Physical examination
	Reproductive health	Reproductive history, symptoms PCOS and sexual health	Self-reported
	Mental health	Anxiety and depression, personality, stress, sleep, traumatic life events and social support	Self-reported
	Lifestyle	Information about weight lost attempts last 4–7 years Diet Physical activity	Self-reported Self-reported Measured by accelerometer and self-reported

PCOS, polycystic ovary syndrome; WOMB, Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both.

the intervention, giving insight into potential gene–environment interactions, personality factors or susceptible socioeconomic groups and ultimately allowing us to refine and personalise future lifestyle intervention programmes to maximally target specific groups.

The main strength of the WOMB project is the fact that it concerns the follow-up of a RCT in which a structured lifestyle intervention was given preconceptionally. We will capitalise on the randomised design in which interference

by other factors, like genetic variability and environmental characteristics, will be balanced between the intervention and the control arm. Inevitably, there will be loss to follow-up, since it is 4–7 years ago that the women were included in the LIFEstyle study. In general, attrition will lead to a reduction in power, and there may be selective attrition reducing the representativeness of the study sample.¹⁶ To control for selection bias, we will always report on the baseline characteristics of those who did and did not participate in

Table 4 Planned measurements of WOMB kids

Phase	Measures		Data type
Between birth and age 3–5 years	Growth	Height, weight and head circumference	Registration municipal youth healthcare visits
	General health	Diseases/health problems, medication and hospital admissions	Parent reported
Age 3–5 years	Demographic variables		Parent reported
	Anthropometrics	Hip, waist and upper arm circumference, height and weight.	Physical examination
	Body composition	Lean body mass, fat mass and total body water	Physical examination
	Cardiometabolic health	Blood pressure, heart rate, arterial stiffness, glucose and insulin levels, lipid profile and inflammatory markers	Physical examination
	General development		Parent reported
	Cognitive and behavioural development	Executive functioning, psychosocial skills and problems, sleep pattern and eating behaviour	Parent reported
		Self-control	Observed in laboratory setting
	Lifestyle	Diet Physical activity	Parent reported Measured by accelerometer

WOMB, Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both.

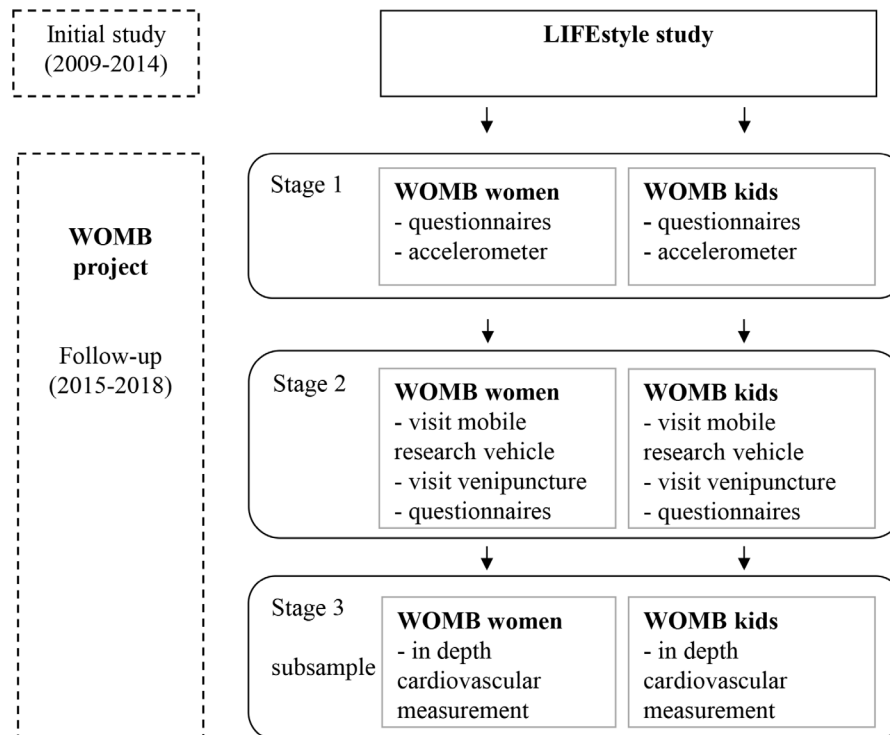


Figure 3 Flowchart follow-up assessment of WOMB project. WOMB, Women, their Offspring and iMproving lifestyle for Better cardiovascular health of both.

follow-up. The original study was not powered on long-term outcome of the women in advance, let alone the follow-up of their offspring, neither was it powered on cardiovascular outcomes. Therefore, we conducted power analyses with respect to the main outcome BMI, which can be considered a risk factor for later CVD.^{17 18} With respect to BMI, we need 90 women in each arm (31.9% of the total population) to detect a 0.5 kg/m² difference (27.5 kg/m² vs 28 kg/m²) with a power of 80% (alpha level of 5% and an SD of 1.2). For the children, the participation rate needs to be higher: 70.1% (214 children), to detect a comparable difference (15.3 kg/m² vs 15.8 kg/m²) with the same power (alpha level of 5% and an SD of 1.3). All in all, power to detect meaningful differences between the groups, especially with respect to secondary outcomes, will depend on the attrition levels. To increase power and generalisability, we are planning to pool data with other studies that use a comparable conceptual framework and an equivalent design and implementation¹⁹ (of which the Finnish RADIEL study is one²⁰).

Ethics and dissemination

Ethics and safety considerations

The study will be conducted according to the principles of the Declaration of Helsinki (revised version of October 2013) and in accordance with the Dutch Medical Research Involving Human Subjects Act.

For WOMB women and WOMB kids separate written informed consents will be obtained, as well as for each follow-up stage. The participants and/or parents will be asked to sign a separate consent form to store biological material in the biobank for up to 50 years. The data will

be handled confidentially and analysed coded, in compliance with the Dutch Personal Data Protection Act.

The study imposes no risks on the participants. Taking a venous blood sample (women 40 mL and children 15 mL) can be a small discomfort for the participants, but is considered safe. In the informed consent, the participants/parents have the ability to choose to participate in the study without blood sampling.

Dissemination

The study findings of the WOMB project will be widely announced and reported to the scientific community, healthcare professionals, policy makers, future parents and general public. Dissemination is crucial in actually achieving the ultimate goal of WOMB project to prevent CVD in two generations by optimising lifestyle of women before and during pregnancy.

The project has a Dutch website mainly focused on participants and a scientifically orientated international website (<http://womb-project.eu/>). In 2015, we started a social media community on Facebook (<http://www.facebook.com/hetwombproject>), primarily directed to Dutch women in the reproductive age group, with the goal to maximally reach our target population at the time that results of the study will be known (2018/2019). This community is regularly fed by interesting news facts, short films about our project, blogs of our researchers and guest blogs of other stakeholders. We will also specifically focus on the dissemination of the study results among nutritionists, general practitioners, midwives and gynaecologists, who are in

the position to advice (future) pregnant women about (pre)conceptional lifestyle.

CONCLUSION

The results of the present ongoing WOMB project, the follow-up of the LIFEstyle study, will show us if a preconception lifestyle intervention can have long-term health benefits for obese women and their children. The project will also provide more detailed information about the relationship between preconceptional diet and physical activity and later health: for the women, but also with respect to the prenatal programming effect on the conceived children. In general, this project will bring forth new knowledge on the prevention of obesity and our opportunities of breaking the intergenerational cycle of obesity and consequent susceptibility for NCDs, including CVD.

Author affiliations

¹Department of Obstetrics and Gynaecology, Academic Medical Centre, Amsterdam, The Netherlands

²Department of Obstetrics and Gynaecology, University of Groningen, University Medical Centre Groningen, Groningen, The Netherlands

³Department of Paediatrics, VU University Medical Centre, Amsterdam, The Netherlands

⁴Department Public and Occupational Health, EMGO Institute for Health and Care Research, VU University Medical Centre, Amsterdam, The Netherlands

⁵Institute of Sport Science, University of Graz, Graz, Austria

⁶Division of Human Nutrition, Wageningen University, Wageningen, The Netherlands

⁷Department of Epidemiology, University Medical Centre Groningen, Groningen, The Netherlands

⁸Department of Obstetrics and Gynaecology, The Robinson Institute, School of Medicine, University of Adelaide, Adelaide, Australia

⁹Division of women and babies, The South Australian Health and Medical Research Institute, Adelaide, Australia

Acknowledgements This follow-up would not have been possible without the original LIFEstyle study. We wish to thank the LIFEstyle researchers and all women who participated in this study. We also want to acknowledge the participating hospitals and staff for their contribution. We are thankful to the lifestyle coaches, research nurses, research midwives and office members of the Dutch Consortium for Healthcare Evaluation and Research in Obstetrics and Gynaecology (www.studies-obsgyn.nl) for their hard work and dedication.

Contributors All authors have contributed to the design and development of the protocol. TJR is the chief investigator of this study. The coordination and drafting of the manuscript was done by CvdB. Critical revision of the manuscript was done by all authors, who also approved the final version.

Funding The LIFEstyle study was supported by a grant from The Netherlands Organization for Health Research and Development (50-50110-96-518). The WOMB project is funded by the Dutch Heart Foundation (2013T085) and the European Commission (Horizon2020 project 'DynaHealth', 633595).

Competing interests None declared.

Patient consent Obtained.

Ethics approval The study was approved by the Local Medical Ethics Committee (UMCG, Groningen, The Netherlands).

Provenance and peer review Not commissioned; internally peer reviewed.

Data sharing statement The WOMBproject group is open to collaboration: in case of data requests, additional analyses or collaborative studies, please contact the WOMB project coordinator (t.j.roseboom@amc.uva.nl).

Open Access This is an Open Access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially,

and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

© Article author(s) (or their employer(s) unless otherwise stated in the text of the article) 2018. All rights reserved. No commercial use is permitted unless otherwise expressly granted.

REFERENCES

1. Mutsaerts MA, Groen H, ter Bogt NC, *et al*. The LIFEstyle study: costs and effects of a structured lifestyle program in overweight and obese subfertile women to reduce the need for fertility treatment and improve reproductive outcome. a randomised controlled trial. *BMC Womens Health* 2010;10:9.
2. Mutsaerts MA, van Oers AM, Groen H, *et al*. Randomized trial of a lifestyle program in obese infertile women. *N Engl J Med* 2016;374:1942–53.
3. van Oers A, Mutsaerts M, Burggraaff J, *et al*. 4: Effects of preconceptional weight loss in subfertile obese women on maternal and fetal outcome. *Am J Obstet Gynecol* 2015;212:S3.
4. Poirier P, Giles TD, Bray GA, *et al*. Obesity and cardiovascular disease: pathophysiology, evaluation, and effect of weight loss: an update of the 1997 American heart association scientific statement on obesity and heart disease from the obesity committee of the council on nutrition, physical activity, and metabolism. *Circulation* 2006;113:898–918.
5. Catalano PM, Ehrenberg HM. The short- and long-term implications of maternal obesity on the mother and her offspring. *BJOG* 2006;113:1126–33.
6. Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiol Rev* 2014;94:1027–76.
7. Poston L, Harthoorn LF, Van Der Beek EM, *et al*. Obesity in pregnancy: implications for the mother and lifelong health of the child. a consensus statement. *Pediatr Res* 2011;69:175–80.
8. Ma RC, Chan JC, Tam WH, *et al*. Gestational diabetes, maternal obesity, and the NCD burden. *Clin Obstet Gynecol* 2013;56:633–41.
9. Herzig K, Danley D, Jackson R, *et al*. Seizing the 9-month moment: addressing behavioral risks in prenatal patients. *Patient Educ Couns* 2006;61:228–35.
10. Lumley J, Chamberlain C, Dowswell T, *et al*. Interventions for promoting smoking cessation during pregnancy. *Cochrane Database Syst Rev* 2009;CD001055.
11. von Elm E, Altman DG, Egger M, *et al*. The Strengthening of Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *Lancet* 2007;370:1453–7.
12. Pi-Sunyer FX. NHLBI obesity education initiative expert panel on the identification, evaluation, and treatment of overweight and obesity in adults - the evidence report. *Obesity Research* 1998;6:51S–209.
13. Kuchenbecker WK, Groen H, Zijlstra TM, *et al*. The subcutaneous abdominal fat and not the intraabdominal fat compartment is associated with anovulation in women with obesity and infertility. *J Clin Endocrinol Metab* 2010;95:2107–12.
14. Kuchenbecker WK, Groen H, Pel H, *et al*. Validation of the measurement of intra-abdominal fat between ultrasound and CT scan in women with obesity and infertility. *Obesity* 2014;22:537–44.
15. Voedingscentrum. Mijn Eetmeter: scan je dagmenu. <https://mijn.voedingscentrum.nl/nl/eetmeter/>
16. Fewtrell MS, Kennedy K, Singhal A, *et al*. How much loss to follow-up is acceptable in long-term randomised trials and prospective studies? *Arch Dis Child* 2008;93:458–61.
17. van Die I, Kromhout D, Geleijnse JM, *et al*. Body mass index and waist circumference predict both 10-year nonfatal and fatal cardiovascular disease risk: study conducted in 20,000 Dutch men and women aged 20–65 years. *Eur J Cardiovasc Prev Rehabil* 2009;16:729–34.
18. Friedemann C, Heneghan C, Mahtani K, *et al*. Cardiovascular disease risk in healthy children and its association with body mass index: systematic review and meta-analysis. *BMJ* 2012;345:e4759.
19. Bangdiwala SI, Bhargava A, O'Connor DP, *et al*. Statistical methodologies to pool across multiple intervention studies. *Transl Behav Med* 2016;6:228–35.
20. Rönö K, Stach-Lempinen B, Klemetti MM, *et al*. Prevention of gestational diabetes through lifestyle intervention: study design and methods of a Finnish randomized controlled multicenter trial (RADIEL). *BMC Pregnancy Childbirth* 2014;14:11.